REMARKS/ARGUMENTS

Applicants respectfully request reconsideration and allowance of this application in view of the following comments. Claims 1, 2, 6, 11-21, 24-27, 43, 45, 47-50, 53-55, 58, 61-63, 65-70, 72-74, and 76-87 were pending. By this Amendment, claims 1, 2, 6, 17-18, 21, 25-27, and 82 have been amended and claims 11-16, 19-20, 24, 43, 45, 47, 48-50, 53, 54-55, 58, 61-63, 65-70, 72-74, 76-77, 79-81, and 84 have been canceled without prejudice or disclaimer. No new matter has been added. Accordingly, claims 1, 2, 6, 17-18, 25-27, 78, 82-83, and 85-87 are pending.

Objection to claim 53

Claim 53 has been deleted without prejudice or disclaimer. It is respectfully requested that the Examiner reconsider and withdraw this objection.

Claim rejections under 35 U.S.C. §112, first paragraph, enablement

Applicants have amended independent claim 1, which now covers a method for determining, ameliorating, and treating heart failure in a human patient, the method comprising the steps of measuring the level of a cytokine or an inflammatory marker or

its production in the blood of the patient, and if such level is elevated, administering to the patient a therapeutically effective amount of a bile acid selected from the group consisting of chenodeoxycholic acid, ursodeoxycholic acid, dehydrocholic acid, and cholic acid. As the Examiner will note, the claim no longer reads on preventing heart failure in a patient comprising administering to the patient any or all compounds. Support for this amendment is found on page 13, lines 7-9.

In support of the view that the amended independent claim is enabled, the following comments are mentioned below. As shown in the specification (reflecting the results of Example 1), the level of endotoxin, LPS, TNFα, and CD 14 are different in patients suffering from chronic heart failure (CHF) compared with healthy individuals. Although the endotoxin production is reduced in patients with CHF without edema, the production of TNFα and CD14 in respect to the endotoxin level is proportionally much higher in the CHF patients than compared with the healthy individuals. Therefore, it is clearly indicated, that the same quantity of LPS distinctly results in the higher production of cytokines in patients suffering from CHF. Furthermore, the overall concentration of endotoxin TNFα and CD14 is largely higher in patients suffering from CHF with edema than in healthy individuals. Thus, Example 1 demonstrates the presence of raised plasma endotoxin concentrations in patients with CHF and peripheral edema. In the presence of unchanged levels of endotoxin binding protein, this reflects a potentially pathogenic situation leading to cytokine induction.

Furthermore, the conclusion of Example 2 in the specification is that UDCA may be tested in patients (with edema or with cardiac cachexia) in comparison with a placebo, that the relationship between LPS plasma levels and prognosis in edematous and nonoedematious heart failure patients may be investigated.

Additionally, Example 10 in the specification shows that LPS-stimulated cytokine production of whole blood can be inhibited by application of UDCA.

In addition, attached are **Exhibits 1** and **2**, which show experiments conducted in vivo for the treatment of chronic heart failure. Also attached is **Exhibit A**, which is a declaration by the inventor of the claimed invention. As stated in the declaration by the inventor, these experiments were conducted based on the teachings of the specification.

Exhibit 1 shows an in vivo study conducted comprising the administration of UDCA to three patients suffering from CHF. This Example clearly provides evidence that administering UDCA ameliorates significantly the overall performance of said patients, particularly in the 6 minutes walking test and the C-reactive protein (CrP)-value.

In another in vivo experiment, **Exhibit 2** shows the importance of a reduction of LPS in patients suffering from cardiovascular and hemodynamic instability.

It should be noted that one skilled in the art would recognize that each of the three additionally claimed bile acids (compared to UDCA) can be used in equal measure, due to their close structural and functional similarity.

Thus, one skilled in the art would conclude with all these examples and based on the teachings of the specification that one can determine, ameliorate, and treat heart failure in a human patient by measuring the level of a cytokine or an inflammatory marker or its production in the blood of the patient, and if any of it is elevated, administering to the patient a therapeutically effective amount of a bile acid selected from the group consisting of chenodeoxycholic acid, ursodeoxycholic acid, dehydrocholic acid, and cholic acid.

It is respectfully requested that the Examiner reconsider and withdraw this rejection.

Claim rejections under 35 U.S.C. §112, first paragraph, written description

As noted above, independent claim 1 has been amended to state a bile acid selected from the group consisting of chenodeoxycholic acid, ursodeoxycholic acid, dehydrocholic acid, and cholic acid. The Examiner main objection seemed to be that independent claim 1 only listed "bile acid," which the Examiner interpreted to mean "any" and "all" bile acid. It is believed that there is adequate description in the specification for the three additionally claimed bile acids (compared to UDCA). It should be noted that one skilled in the art would recognize that each of the three additionally claimed bile acids (compared to UDCA) can be used in equal measure, due to their close structural and functional similarity.

It is respectfully requested that the Examiner reconsider and withdraw this rejection.

New matter rejection under 35 U.S.C. §112, first paragraph

Support for claim 78 is found in the specification on pages 6 and 7 of the specification for "bile acid" and a "diuretic."

It is respectfully requested that the Examiner reconsider and withdraw this rejection.

Claim rejections under 35 U.S.C. §102(b)

The Examiner rejected claims 53, 57-58, 72-73 as being anticipated by EP 0528312A1.

Independent claim 53 has been canceled without prejudice or disclaimer. In addition, the dependent claims from 53 have also been canceled without prejudice or disclaimer.

It is, therefore, respectfully requested that the Examiner reconsider and withdraw this rejection.

Rejection of claims 82-87 under 35 U.S.C. §103(a) over Kocsar et al in view of EP 0528312

In order to show obviousness, the combined references must teach or suggest every element of the claimed invention and there must be motivation or suggestion to modify the reference. The combined references fail to teach or suggest 1) a method of reducing elevated levels of lipopolysaccharide (LPS) in human blood of patients 2) by administering an amount of bile acid selected from the group consisting of ursodesoxycholic acid, chemodeoxycholic acid, dehydrocholic acid, and cholic acid effective to reduce the elevated levels of LPS in human blood of patients as in claim 82. Kocsar namely mentions administering the bile acid deoxycholate, which is not claimed in claim 82 and the EP reference discloses a pharmaceutical formulation containing a mixture of bile acids and their salts with alkali metals or organic bases (See claim 1). Furthermore, there is no motivation or suggestion to modify the bile acid in Kocsar with the specific bile acids claimed in claim 82 (e.g. different structure). Thus, the combined references do not render the claimed invention obvious.

It is respectfully requested that the Examiner reconsider and withdraw this rejection.

CONCLUSION

Based on the foregoing remarks it is believed that the claims are in condition for allowance.

Respectfully submitted,

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